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ance. Serum of pregnant women is most convenient to detect doubtful reliability. For this reason at least close co-operation between the physician and the serologist is absolutely desirable. The serologist should have short clinical records with regard to syphilis and to other diseases or pregnancy. Otherwise he works to a certain degree "in the dark" and will not be able to recognise when his tests are not correctly adjusted. The physician also should be aware of this situation and of the advantage of co-operation. He should not hesitate to inform the serological laboratory of the clinical diagnosis and the peculiarities of his case. Since an increase of lability may exist only for a limited period in some infectious diseases or in other conditions, in doubtful cases, it is desirable to repeat the examination of the blood at due intervals and to rely on the positive result only if it is continual. It should be realised that non-specific reactivity may result at present from another reason as in the early days of the Wassermann reaction. At the beginning the test was performed quite empirically without any knowledge of the peculiarities to be considered. To-day, however, the endeavour to increase the sensitivity is attended by a danger of passing the border-line which limits the reactivity characteristic of syphilis.

In any case it is of the greatest significance to know the two possibilities of serological reactivity, one (the syphilitic type) caused by antibody action, the other (general biological type) dependent on non-specific blood alterations. Both may induce the same result (complement fixation or flocculation, in serological syphilis tests. Their differentiation is the most important progress in the knowledge of the serology of syphilis. Only the due consideration of these two mechanisms independently of one another may guarantee the correctness of serological work and its practical application.

My thanks are due to the Medical Research Council of Ireland for the grant which has enabled me to continue my work. I am very grateful also for the hospitality of the School of Pathology, Trinity College, and for the facilities afforded by Professor O'Meara in the Department of Bacteriology.

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### VI

## NON-GONOCOCCAL URETHRITIS \*

By WING-COMMANDER G. L. M. McELLIGOTT

My contribution to this discussion is not so much to shed any fresh light on a condition of so mixed an ætiology as non-gonococcal urethritis, as to stimulate discussion on the subject, so that by the ventilation of our pooled experience there may emerge some degree of uniformity of opinion as to what are the most efficient and expeditious methods of treatment for this all too common condition.

In 1932 Harkness read a paper before this society on this very subject which was subsequently published in this Journal in March,

\* An address delivered to the Medical Society for the Study of Venereal Diseases, May 30th, 1942.

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1933, and though it was written in pre-sulphonamide days the article still repays careful study ; it provides by far the most comprehensive classification of the many possible causes of this condition and indicates lines of treatment that are as important to-day as they were then.

Formerly, when it was usual to give far longer courses of chemotherapy than are now thought necessary, a certain proportion of non-gonococcal cases appeared to be cured *pari passu* with the gonococcal ones, but so great was the enthusiasm for the new drugs as cures for gonorrhœa, that little interest was taken in their effects on a condition that often recovered spontaneously within three or four weeks. In the Services, however, non-gonococcal cases are in a sense as important as gonococcal ones, as they are required to be hospitalised until they are clinically cured, with the result that their stay in hospital is often considerably longer than that of the gonococcal cases. This was very well illustrated in a paper by Lt.-Col. King and Major Williams in the Journal of the R.A.M.C. of August, 1941, recording the results of the treatment of this condition with sulphapyridine.

Of 98 patients treated intensively, 3 became seriously ill and are not included, 27 needed no additional treatment with an average stay in hospital of 13 days, 7 required a small amount of additional treatment (average 23 days), the remaining 61 required a good deal more treatment with an average of 48 days in hospital. Of those treated non-intensively with a routine 14-day course, 34 required no additional treatment with an average stay of 21 days, 6 required a small amount of additional treatment (average 26 days), and 57 needed much more treatment with an average stay of 60 days. These figures which are in line to some extent with my own experience, show fairly conclusively that the original impressions of the efficacy of the sulphonamides in most cases of non-gonococcal urethritis were largely illusory, and that many workers, myself included, were dazzled by the dramatic effects of the drugs in a small proportion of cases, some of which were doubtless chronic gonococcal infections not showing obvious gonococci, and the remainder probably mostly due to coliform organisms, which are equally susceptible to the sulphonamides.

As is well known, the flora found in non-gonococcal discharges is varied, but generally remarkably constant, though one or other type usually predominates in the smear. It is not particularly helpful to know that some of these organisms are also present in the healthy fossa navicularis and even in the apparently healthy vagina. Among those most often seen in smears are staphylococci, streptococci of the faecal type, diphtheroids, coliform organisms, diplococci and diplobacilli, Gram negative and Gram positive, each far larger than the gonococcus, and very small Gram negative micrococci. Is it considered that all, some, or even none of these organisms are pathogenic, or is it at all likely that a virus akin to those causing lymphogranuloma inguinale, trachoma, or penile papillomatosis, which last condition not uncommonly accompanies a non-gonococcal urethritis or a secondarily infected gonococcal one, is sometimes responsible? With regard to trichomonad infestations of the male urethra, I must admit that my own efforts to find this organism have been singularly unsuccessful. It is noteworthy too that there is no record of any animal experiment with the common infecting organisms, nor up to the present, except in

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the case of staphylococci, fæcal streptococci, and coliforms, any attempt to assess their susceptibility to sulphonamides *in vitro*.

Non-gonococcal urethritis is a common condition, and American and British statistics indicate that at least 30 per cent. of all cases of urethritis are of this nature. The high incidence is more noticeable in the Services as all cases of urethritis are referred to a specialist for treatment, whereas in civil life the general practitioner, on receipt of a negative report on a smear, often either elects to treat the case himself or not to treat it at all, merely reassuring the patient that the condition will get well in time, which indeed it often does. In this disease, as in many others, time will often prove to be the great healer and in a high proportion of cases the condition will clear up spontaneously in about a month or less, irrespective of the nature of the therapy exhibited by the doctor, always provided that this itself is innocuous.

But for the Services this state of affairs is not good enough, involving as it often does a far longer stay in hospital for a comparatively trivial complaint, while the treatment of the more serious one is more effective and far more expeditious. It is my hope that in the future we shall avoid the tendency to group together for purposes of treatment all these cases of non-gonococcal infection and that even now some attempt should be made to collate the history and the clinical signs with what is seen in the smear and the culture. My own experience with the last has been singularly disappointing, the culture usually merely acting as a lens which magnifies though hardly ever increases the knowledge which has been gained by careful perusal of the slide.

May I indicate my own procedure in investigating and treating what is apparently at first sight a case of primary non-gonococcal urethritis. In this, as in all conditions of uncertain ætiology, careful history taking is essential, and when gonococci are not obvious in the smear, the usual clinic questionnaire will need considerable amplification. Careful attention must be paid to any previous history of discharge, dysuria, hæmaturia, frequency, perineal pain or discomfort, as well as a frank story of "cured" gonorrhœa even many years ago. The mention of any of these will immediately lead one to suspect that the condition is not primary at all, but a relapse of a previous infection, probably gonococcal and it is also, of course, an indication that a G.C. Fixation test and a search for the focus of infection are essential, and that cultures of the prostatic-vesicular secretion and the urethral discharge are desirable.

If, however, as is often the case, no previous history can be obtained, the mode of onset of the condition will need careful investigation. How long has the patient noticed the discharge? Was there any preceding pain, discomfort or malaise or is there any now? What was his previous occupation? Was it sedentary or otherwise and does he feel or has he felt "out of sorts?" Finally, the dates of any recent risks of infection, marital as well as extramarital, should be noted, the health of the wife or consort enquired into, and also the nature of any chemical prophylaxis or contraceptive used. After a specimen of the discharge has been collected, the urine is examined in two glasses, its reaction is noted, and a small specimen from the second glass is tested for sugar, especially if there is any accompanying

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balanitis. The information gathered from the history is then collated with any derived from the slide and the urine. Thus, a man with a sedentary occupation, who may or may not have run a recent risk of infection, feels a little "out of sorts" and notices a slight discharge; the first and probably the second glass of urine is cloudy, hazy, or perhaps only faintly opalescent. This patient's smear will as often as not show coliform organisms predominating, and a culture of a mid-stream specimen will confirm a diagnosis of *Bacillus coli* cystitis with or without an accompanying pyelitis. Or again, the young married Serviceman, recently returned from leave in the best of health, notices a urethral discharge and consults his medical officer often apprehensive as to his wife's fidelity. The smear is examined and though pus cells are abundant, there is a striking absence of organisms of any sort. A question as to the type of contraceptive used will frequently divulge that quinine pessaries have been lavishly employed. These findings and such a history strongly suggest the diagnosis of chemical urethritis. As is well known this condition is sometimes brought about by chemical prophylaxis. When 33 per cent. calomel ointment is instilled into the urethra in large and repeated doses both before and after intercourse the findings, if not the history, will be identical with those in the case quoted. It must be remembered that a bacterial vaginitis will sometimes occur in women as a direct result of what was originally a chemical one, the vaginal and possibly other flora having become pathogenic on a devitalised and possibly eroded mucous membrane, and that the male consort may become infected therefrom; also it is not unreasonable to believe that in some cases this may well be the starting point of many severe trichomonad infestations.

In most cases, however, the story is a simple one. There is no previous history; there was a risk of infection some days or weeks ago with a comparatively unknown woman, and there is some slight dysuria, a "dirty" first glass of urine and a muco-purulent discharge similar to that of an early case of gonorrhœa. Yet repeated smears show no gonococci, but in addition to pus cells, a variety is found of what are most often referred to as "other organisms." As is well known the posterior as well as the anterior urethra can become infected and littritis, prostatitis, vesiculitis and epididymo-orchitis are not very unusual local complications. Strangely enough I have yet to see a case of prostatic or periurethral abscess which did not at some date follow a gonococcal infection, though in women non-gonococcal abscesses of Bartholin's glands are not uncommon. Tuberculous epididymitis is not so very uncommon and in all cases where the mid-stream specimen is sterile, especially when the second glass of urine is hazy or cloudy, the centrifuged deposit from a twenty-four-hour specimen should be carefully examined for tubercle bacilli.

Metastatic infections are not very common but I have seen several cases of severe arthritis accompanying a primary non-gonococcal urethritis with a persistently negative G.C.F.T., two of which were accompanied by the so-called Keratoderma blenorrhagica. The arthritis, which clinically is indistinguishable from the gonococcal variety, is often accompanied by a metastatic conjunctivitis or an iritis. These sometimes resist treatment for long periods, though I

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remember one case of severe iritis, in which a streptococcus of low virulence was grown from a midstream specimen, where the effect of sulphapyridine was dramatically immediate.

Up to about six months ago I treated these cases with sulphonamides as a routine. With few striking exceptions the immediate results were disappointing, but the great majority were discharged from hospital signless and symptomless after three or four weeks. Various schemes of treatment were tried and the best results followed a nine-day course of sulphanilamide, four grams daily, accompanied by irrigations of the whole urethra with 1/10,000 oxycyanide of mercury. During this period we were constantly reviewing and revising the treatment of our gonococcal cases, with the result that the duration of treatment was lessened and the results greatly improved, but it became increasingly noticeable that no such improvement took place in the non-gonococcal cases and the former apparently short stay in hospital, now seemed by comparison to be rather depressingly long. Strangely enough the cases which appeared to benefit most from chemotherapy were those in which the second glass of urine was hazy on first examination. This may be either because the infection had been of longer standing than the patient would admit, and that some acquired immunity was helping an otherwise subefficient bacteriostatic agent, or that, in spite of the inconclusive nature of the urethral smear, the *Bacillus coli* or perhaps even the gonococcus was the active if not the obvious cause. I have for some time noticed that in many of these cases the history suggests an incubation period of anything from three to five weeks, but I have usually suspected this story to be an attempt to conceal a delay in reporting sick or that they have unsuccessfully attempted to treat themselves. Recently however, colleagues working in other Service clinics have noticed the incubation periods of these infections to be uniformly longer than those in gonococcal ones. On the assumption that in most cases the infection is of longer standing than the duration of symptoms would indicate, they claim that in the absence of prostatic involvement, they obtain the best results when the urethra is massaged over a metal bougie as early as the third and sixth days of an immediate course of a sulphonamide preparation, and that they have met with no ill effects following this somewhat unorthodox treatment.

The present therapeutic problem seems chiefly to turn on the questions: (1) Should sulphonamides be given as a routine? (2) Which is the most efficient drug for the purpose and what is the optimum dosage and period of administration? (3) What, if any, adjuvant treatment is necessary?

In spite of the fact that the immediate results of chemotherapy are often disappointing and that, as Harkness told us nine years ago, many cases will be cured by abstinence from alcohol, an increased fluid intake, and careful irrigation of the whole urethra with a warm weak antiseptic solution such as oxycyanide of mercury, 1/10,000, I feel that in our present state of ignorance and with the knowledge that a small proportion of these cases are caused by gonococci or coliform organisms, in spite of the fact that these organisms are not obvious in smears, it is probably safer to institute sulphonamide therapy in every case. The expectation that sulphathiazole with its reputed

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anti-staphylococcal action would be more effective than other preparations has not been fulfilled, and probably the best practice is to give sulphapyridine as for a gonococcal infection.

Adjuvant treatment will be necessary in most cases and should be confined to simple irrigation of the whole urethra with oxycyanide of mercury, 1/10,000. It is probably better not to commence irrigation until two days after the start of chemotherapy, as it is then possible after repetition of the smears to assess to some extent the effect, if any, of the drug. If at the end of ten days' irrigation there is no considerable improvement, the possibility of a badly draining focus of infection should be considered and a full investigation of the prostatic-vesicular secretions and of the anterior urethra should be carried out.

It is tempting to give a mixed vaccine from the commencement and to deceive oneself that it is doing some good, but as it is known that vaccines at their best are a slow-acting form of therapy and it will be difficult to assess whether any improvement is "post hoc" or "propter hoc," their use is best reserved for resistant cases. It is possible in the absence of a more detailed knowledge of these infections and more certainly efficient chemotherapeutic drugs, that immediate hyperthermic pyretotherapy would give the quickest and best results. I have not noted any immediate improvement after further chemotherapy following intravenous T.A.B. vaccine, such as occurs in initially resistant gonococcal cases, and even the metastatic complications do not react as well as those known to be due to the gonococcus.

As most of these cases follow intercourse, it seems reasonable to classify them among the venereal infections, and though I have not recently had the opportunity of examining many female consorts, I feel that in the large majority chronic cervicitis would be a fairly constant finding. This condition of course can have many possible causes, chief among which in young nulliparous women are the following:—

(1) Previous gonococcal cervicitis treated with sulphonamides, in which the condition is perpetuated by secondary organisms which are not susceptible to these drugs.

(2) Previous primary infection, venereal or otherwise, with pathogens other than gonococci.

(3) Unclean and careless methods of douching, whereby the cervix is first abraded and then infected with secondary organisms.

(4) The growing use of the internal menstrual tampon, which might easily abrade the cervix and which, when saturated with menstrual blood, will act as an ideal culture medium for any organisms which may be introduced therewith.

(5) Previous instrumental interference with the cervix.

It is outside the scope of this paper to discuss how this condition is best treated, but it is suggested that everything should be done to persuade the consorts of male non-gonococcal cases to report for examination, and it is hoped that clinic medical officers will cheerfully take on the task of investigating, advising and treating these cases, as if they don't, it seems that nobody else will.

With the advent of the sulphonamide drugs and their proved efficacy in both male and female cases of gonococcal infection, there is a tendency to neglect the secondary cervicitis which sometimes continues

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for a long time after the cure of the gonorrhœa. It seems that this secondary infection, as like as not with sulphonamide resistant organisms, is well nigh inevitable, but it is debatable whether the condition will clear up properly without adequate local treatment. My own experience leads me to think that usually it will not do so, and in many of my own cases the initial week of chemotherapy is followed by two, three or four weeks of local treatment before the cervix and its secretion approach the normal. The subject of non-gonococcal vaginal discharges to be discussed at a future meeting of this society, has a direct bearing on the problem of non-gonococcal urethritis in men.

### VII

#### NON-GONOCOCCAL URETHRITIS \*

By I. N. ORPWOOD-PRICE, M.R.C.S., L.R.C.P., D.P.H.

I UNDERSTAND that there has been a high incidence of non-gonococcal urethritis in the Services, more particularly in the Royal Air Force. In order to gain some idea as to whether this increase has its counterpart in civilian life I have examined the records of two clinics—Whitechapel and University College Hospital. The figures which are for July–December, 1941 inclusive, are as follows :—

#### PROPORTION OF GONOCOCCAL AND NON-GONOCOCCAL URETHRITIS

	Whitechapel Clinic	University College Hospital Clinic
Non-gonococcal urethritis		
Total cases . . . . .	73 (21·3%)	26 (17%)
Cases with previous history of gonorrhœa . . . . .	34 (46%)	8 (30·8%)
Gonococcal urethritis . . . . .	270 (78·7%)	127 (83%)

The percentage figures of these two clinics agree fairly well, in spite of the fact that the patients of each are, on the whole, drawn from different social strata. They do not show any appreciable increase in the number of cases suffering from non-gonococcal urethritis. An interesting point is that, almost half of the patients suffering from non-gonococcal urethritis will admit a previous attack of gonorrhœa. (According to Pelouze, this state of affairs obtains in U.S.A., 333 N.V.D. urethritis, of which 193 admit previous gonorrhœa.)

\* An address to the Medical Society for the Study of Venereal Diseases, May 30th, 1942.